REMARKS

The only issues outstanding in the Office Action mailed December 6, 2007, are the rejections under 35 U.S.C. 102 and 103. Reconsideration of these issues, in view of the following discussion, is respectfully requested.

Claims 1-7 and 10 have been rejected under 35 U.S.C. 102(b) or, in the alternative 103, over Cramer (U.S. Application 2001/0047086). Reconsideration of this rejection is respectfully requested.

It is argued, at page 2 of the Office Action, that "if a difference exists between the claims and Cramer…it would reside in optimizing the steps of Cramer…". Applicants respectfully disagree with this analysis. Cramer is directed to a method for screening "displacer candidates" for use in displacement chromatography. Patentees state, at paragraph [0005], that

> "displacement chromatography is fundamentally different from elution chromatography (e.g., linear gradient, isocratic or step gradient chromatography). The displacer, having an affinity higher than any of the feed components, competes effectively for adsorption sites on the stationary phase. An important distinction between displacement and desorption is that the displacer front always remains behind the adjacent feed zones in the displacement train, while desorbents (e.g., salt, organic modifiers) move through the feed zones. The implications of this are quite significant in that displacement chromatography can potentially concentrate and purify components from mixtures having low separation factors. In the case of desorption chromatography, however, relatively large separation factors are generally required to give satisfactory resolution."

Applicants moreover state that, "the essential operational feature which distinguishes displacement from elution or desorption chromatography is the use of a displacer molecule. See paragraph [0006] of the application.

By contrast, the present claims are directed to a method for discovering suitable *elution* chromatography parameters for the separation of biological molecules, in an automated manner.

In contrast to the teaching of Cramer, the matter of the present invention is based on methods of elution chromatography and it is the aim to develop a simple method to find out with minimal effort optimized conditions for purifying biological samples, preferably for the separation of biological molecules. The present invention is focused on and claims methods of ascertaining conditions of the elution chromatography. This means that, in each case, the biological samples are bound to the chromatography media. Then materials (solutions and substances) are added, which are able to desorb (to elute) the biological sample from the chromatography medium in a way as described on page 3, last paragraph of the present specification. The biological sample is removed from the chromatography material but is not displaced by a further compound, unlike the situation in displacement chromatography as in Cramer.

Because the present invention involves a method for the purification of biological samples and isolation of biological molecules in large scale, the chosen chromatography material has to be useable continuously for the purification or separation in an ongoing process. Therefore, conditions of displacement chromatography would not be suitable. Thus, Cramer, which clearly distinguishes elution chromatography from their method, does not anticipate the present claims, nor suggest them. One of ordinary skill in the art would not transfer any teachings from the displacement method of Cramer to elution chromatography, in view of the above discussed substantial differences in materials, technique and conditions.

By way of further explanation, the divergent techniques can be explained as follows.

There are three different types of liquid chromatography: 1.) isocratic elution, 2.) elution chromatography and 3.) displacement chromatography.

These types of chromatography are each carried out in entirely an different technical manner; moreover the basic physico chemistry which leads to separation is different. In the case of isocratic elution the compounds to be separated are divided from one another according to their affinities for a stationary phase and for the mobile phase. Molecules with high affinity for the stationary phase move with less speed across the column than molecules with low affinity, because the probability of residence of molecules with high affinity for the stationary phase is higher than that for molecules which stay in the mobile phase. In consequence, the molecules are eluted according to a Gaussian bell curve.

The separation mechanisms in elution chromatography are the same as described for the isocratic elution of compounds, but with the difference that during the course of separation a second mobile phase is added. This secondary mobile phase speeds up the elution of molecules from the stationary phase by weakening or preventing the interaction between the molecules and the stationary phase. This effect is also achieved if the second mobile phase is added in big excess. Molecules of the second phase in excess shield the sample molecules, which shall be separated, from the interaction with the stationary phase. The effect is a decrease of the probability of residence of molecules with high affinity for the stationary phase and a decrease of affinity for the stationary phase.

On the other hand, in separation carried out by means of displacement chromatograpy, the affinity for the stationary phase stays the same during the whole separation procedure, because the separation is carried out with only one mobile phase. In displacement chromatography, a molecule with high affinity for the stationary phase or chromatography matrix (the displacer) competes effectively for bonding sites, and thus displaces all molecules with lesser affinities for the stationary phase. In order to elute the molecules, which interact with the stationary phase is added to the eluent in low concentration. This second molecule displaces the desired molecule from the stationary phase. The desired molecules cannot return to the bonding sites if the displacer molecules follow directly. This means, that molecules with higher affinity displace molecules with less affinity for the stationary phase.

In contrast to the mechanism of elution chromatography, in displacement chromatography the desired molecules of the sample and the displacer molecules compete for the bonding sites of the stationary phase. In order to achieve a good separation result the flow rates during displacement chromatography are reduced to a tenth of the separation techniques described above. Because of the separation mechanism during displacement chromatography the affinity for the stationary phase plays a minor role, unlike elution chromatography, where affinity for the stationary phase dominates.

The disclosure of Cramer deals with the physico chemical laws of displacement chromatography, but disregards the principles of elution chromatography. According to the teachings of Cramer, the skilled artisan is able to find suitable displacers, but gets no information

allowing selection of suitable parameters for elution chromatography, as claimed in the present application. Therefore, the teaching of the present application is in no way an "optimization" of the steps of Cramer.

Accordingly it is submitted that claims 1-7 and 10 are in no way anticipated, nor suggested by the disclosure of Cramer, and withdrawal of these rejections is respectfully requested.

Claim 5 has also been rejected under 35 U.S.C. 103 over Cramer taken with each of MacPhee (U.S. Patent No. 2003/0161753), Snyder (U.S. Patent Publication No. 2005/0182242), and Pantoliano (U.S. Patent No. 6,214,293). Reconsideration of these rejections is also respectfully requested. None of the cited references remedy the above-noted deficiency of Cramer, in that none suggest modifying the disclosure of Cramer so as to conduct elution chromatography, regardless of any other teachings that the references might provide. Accordingly, for the same reasons that the above noted rejections fail, the rejection of claim 5 must also be withdrawn. The same is respectfully requested.

Finally, with respect to the restriction requirement, it is again maintained that the restriction should be withdrawn, for the reasons set forth at page 8 of Applicants prior reply. The argument at page 3 of the present Office Action, that claim 8 is obvious or anticipated over Cramer, is discussed above. In view of that discussion, it is clear that the restriction requirement should be withdrawn.

The claims of the application are submitted to be in condition for allowance. However, should the Examiner have any questions or comments, he is cordially invited to telephone the undersigned at the number below.

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,

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